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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/589,956	09/20/2007	Edward H. Cohen	C007-7022US0	2118

56679 7590 09/25/2009

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EXAMINER	
HADDAD, MAHER M	
ART UNIT	PAPER NUMBER
1644	
MAIL DATE	DELIVERY MODE
09/25/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/589,956	COHEN ET AL.	
	Examiner	Art Unit	
	Maher M. Haddad	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 August 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-33* is/are pending in the application.

4a) Of the above claim(s) *12-33* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-11* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1-33 are pending.

2. Applicant's election with traverse of Group I, claims 1-11, drawn to a protein comprising HC and LC that binds to an activated conformation of LFA- 1, filed on 8/06/009, is acknowledged.

Applicant's traversal is on the grounds that the groups of claims are interrelated and can be conveniently searched in one location. In this regard, it is noted that the search class and subclass for each group has not been specifically identified in the restriction requirement. This is not found persuasive because Applicant's inventions do not contribute a special technical feature when viewed over the prior art they do not have a single general inventive concept and so lack unity of invention as set forth in the previous Office Action.

The requirement is still deemed proper and is therefore made FINAL.

3. Claims 12-33 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to nonelected inventions.

4. Claims 1-11 are under examination as they read on a protein comprising HC and LC that binds to an activated conformation of LFA- 1.

5. There appear to be discrepancy between the Sequence Listing and the specification. For example:

A. Claim 5 recites (Xa-S-X2-D-X4-X5-S-X7-A-X8-X9-X10-X11 as SEQ ID NO: 4 (a 13 amino acid (aa) sequence), however, the Sequence Listing lists that SEQ ID NO: 4 is a 31 amino acid sequence

B. The specification on pages 88 and 89, indicates that SEQ ID NO: 41 and 42 is a nucleic acid sequence, however, the Sequence Listing lists SEQ ID NO: 41 and 42 as an amino acid sequence.

C. The specification discloses that SEQ ID NO: 61 (477 aa long) at positions 114-115 are MV (see page 96), however, the Sequence listing list SEQ ID NO: 61 (476 aa long) at the same positions as N.

D. The specification discloses that SEQ ID NO: 60 at position 116 is I (see page 95), however, the Sequence listing list SEQ ID NO: 60 at the same positions as L.

E. The specification discloses that SEQ ID NO: 37 (117 aa long) (see page 86), however, the Sequence listing list SEQ ID NO: 37 (120 aa long) by adding positions 113-115 as XAA.

F. The specification discloses that SEQ ID NO: 36 (see page 86) with positions 59-60 as YY, however, the Sequence listing list SEQ ID NO: 36 with positions 59-60 as TI.

G. The specification discloses that SEQ ID NO: 35 (106 aa long) (see page 85), however, the Sequence listing list SEQ ID NO: 35 (114 aa long) by adding multiple amino acids.

H. The specification discloses that SEQ ID NO: 34 (111 aa long) (see page 85), however, the Sequence listing list SEQ ID NO: 34 (110 aa long) by deleting an amino acid.

I. The Sequence Listing refers to SEQ ID NO: 33 as a 115 amino acid sequence, wherein Xaa can be any naturally occurring amino acid. While in the specification, SEQ ID NO:33 is represented on page 85 as a 109 amino acid sequence with no Xaa.

J. Applicant is required to check all the sequences in the specification and claims to make sure that they do correspond to the sequences in the Sequence Listing.

6. Claim 11 is objected to for the following informalities: the claim number "11," should be "11."

7. The following is a quotation of the second paragraph of 35 U.S.C. 112.

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

8. Claims 1-11 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A) Claims 1-4 are indefinite in the recitation of "D2-57, DX-2001, C1-54 or P1-G10" because its characteristics are not known. The use of " D2-57, DX-2001, C1-54 or P1-G10" Fab antibody as the sole means of identifying the claimed antibody renders the claim indefinite because " D2-57,DX-2001, C1-54 or P1-G10" is merely a laboratory designation which does not clearly define the claimed product, since different laboratories may use the same laboratory designations to define completely distinct hybridomas or cell lines. It is suggested that a deposit number be cited in the claims.

B) The recitation "D2-57, DX-2001, C1-54 or P1-G10 antibody" in claims 1-4 is ambiguous. Given that D2-57 antibody was fished from Fab phage library (see page 83, line 24), it is not clear whether the D2-57 recited in the claim refers to antibody fragment (Fab) or refers to the converted D2-57 IgG1 recited on page 92, line 8.

C) Claim 1(v-vi) is indefinite, ambiguous and unclear. It is unclear how the nucleic acid that hybridizes (antisense) to a sequence that encodes the heavy/light chain domain of the D2-57, DX-2001, C1-54 or P1-G10 (sense) would encode a heavy/light chain variable domain sequence. The resultant antisense sequence would not encode a heavy/light chain variable domain.

D) The recitation of "hybridizing under stringent conditions" in claim 1(v-vi) is ambiguous. Although the specification discloses on page 30, 2nd ¶ general parameters for calculating such conditions, in the absence of a clear definition of the metes and bounds of this phrase it is unclear which conditions are actually claimed. It is suggested that Applicant amend the claims to recite a particular set of hybridization and wash conditions, such as those exemplified on page 30, 2nd ¶ of the specification, to overcome this rejection.

E) The recitation of percentage identity "80/85/90% identical" in claims 1(iii-iv), 3, 4, without setting a structural feature for the comparison is indefinite.

F) The recitation "Xa-S-X2-D-X4-X5-S-X7-A-X8-X9-X10-X11 (SEQ ID NO: 4)" in claim 5 is indefinite. There are two different SEQ ID NO: 4, the one listed in the claim and the one listed in the Sequence Listing. It is not clear which SEQ ID NO: 4 is being claimed.

9. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

10. Claims 1-11 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

It is apparent that the cell lines that produces the anti-activated LFA-1 Fabs, D2-57, DX-2001, C1-54 are P1-G10 are required to practice the claimed invention. As a required element, it must be known and readily available to the public or obtainable by a repeatable method set forth in the specification. If it is not so obtainable or available, the enablement requirements of 35 USC 112, a deposit of the cell line, which produces this antibody, may satisfy first paragraph. See 37 CFR 1.801-1.809.

If the deposits have been made under the terms of the Budapest Treaty, an affidavit or declaration by applicants or someone associated with the patent owner who is in a position to make such assurances, or a statement by an attorney of record over his or her signature, stating that the cell line has been deposited under the Budapest Treaty and that

the cell lines will be irrevocably and without restriction or condition released to the public upon the issuance of a patent would satisfy the deposit requirement made herein. See 37 CFR 1.808. Further, the record must be clear that the deposit will be maintained in a public depository for a period of 30 years after the date of deposit or 5 years after the last request for a sample *or for the enforceable life of the patent whichever is longer*. See 37 CFR 1.806. If the deposit has not been made under the Budapest treaty, then an affidavit or declaration by applicants or someone associated with the patent owner who is in a position to make such assurances, or a statement by an attorney of record over his or her signature must be made, stating that the deposit has been made at an acceptable depository and that the criteria set forth in 37 CFR 1.801-1.809, have been met.

If the deposits were made after the effective filing date of the application for a patent in the United States, a verified statement is required from a person in a position to corroborate that the cell line described in the specification as filed are the same as that deposited in the depository. Corroboration may take the form of a showing of a chain of custody from applicant to the depository coupled with corroboration that the deposit is identical to the biological material described in the specification and in the applicant's possession at the time the application was filed.

Further, amendment of the specification to disclose the date of deposit and the complete name and address of the depository (ATCC.10801 University Boulevard, Manassas, VA 20110-2209) is required as set forth in 37 C.F.R. 1.809(d).

11. Claims 1-11are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicant is in possession of an anti-activated LFA-1 antibody comprising VH and/or VL of SEQ ID NOS: 34/33, 36/35, 38/37 or 61/60 (listed on page 85-86 of the specification); or an anti-activated LFA-1 antibody comprising VH CDR1-3 of SEQ ID NOS: 1-3 and VL CDR1-3 of SEQ ID NOs:7-9. or an anti-activated LFA-1 antibody D2-57, DX-2001, C1-54 or P1-G10 (once the deposit is satisfied).

Applicant is not in possession of the protein claimed in claims 1-11.

The scope of the claim encompasses antibodies with 6 intact CDRs as well as a subgenus of antibodies that encompass variation (fragments and/or analogs) in the 6 CDRs and framework. A subgenus of antibodies that encompass up to 10% to 20% variation in the VH and/or VL. A subgenus of antibodies that encompass up to 9 amino acid variations in the VH CDR3 of SEQ ID NO:4. A subgenus of antibodies that encompass less than the full amino acid sequence of the VH CDR1-3 and/or VL CDR1-3 (i.e., 3/5, 13/17, 8/11, 7/11, 4/7 and/or 5/8, respectively.

Prior art discloses 6 CDRs as being essential structure of the antibody's binding site, and thus when intact, would provide enough structure to define the antibody's binding site (structure / function correlation) e.g. where amino acid substitutions can be made so as to change (e.g. 6 CDR's) or retain (e.g. constant or variable framework) antigen binding. However, prior art teaches that variation(s) within the CDRs render antigen binding unpredictable. Therefore, a single antibody species (D2-57) would not be deemed by one of skill in the art to be representative of a claim that defines an antibody that binds activated LFA-1 comprising at least 80-90% identity to the VH and VL chains in D2-57, DX-2001, C1-54 or P1-G10.

The specification provides four anti-activated LFA-1 antibody which was not random combinations of VH and VL i.e., it had specific VH domain (SEQ ID NO: 36-38 and 61) paired with specific VL domain (SEQ ID NO: 33-35 and 60). No other VH domain was provided that share the less than the full length of all CDR1-3 of SEQ ID NO: 1-3 or the full length of all VL CDR1-3 of SEQ ID ON:7-9. The state of the prior art (see e.g. Klimka et al., British Journal of Cancer (2000) 83:252-260, and Beiboer et al., J. Mol., Biol. (2000) 296:833-849) is that methods for screening rely on a two step process where each step results in an antibody. However, each step requires one of the variable domains to be a defined sequence and the defined variable domain provides enough structure to obtain an antibody. The prior art methods do not result in an antibody solely by keeping only one CDR in the VH/VL defined and randomized the rest of the VH and VL domains. The prior art indicated that, in some instances, the CDR3 region is important. However, this region is not solely responsible for binding. The conformation of the other CDRs, as well as framework residues influence binding.

However, neither the specification, nor the prior art provides any examples to support the premise that only one CDR of the VH or VL is solely responsible for antigen binding. The prior art does not support a definition of an antibody structure solely by defining the CDR sequence of a VH or VL. Accordingly, the disclosed species would not be deemed by one of skill in the art to be representative of the claim scope. The claims do not meet the requirement s of 35 USC 112, first paragraph for written description.

The claims encompass antibodies in which modification of the amino acids may vary in either or both the VH and/or VL regions of D2-57, DX-2001, C1-54 or P1-G10 via addition, deletion, substitution or insertion of one or more amino acids.

The instant application encompasses (but does not exemplify) fragments and analogs (deletion/addition/substitution) to the claimed antibody. The specification discloses that the variation in the VL/VH depends on the germline sequence. There is teaching identifying what amino acids can be varied within the VL or VH antibody regions and still retain specific binding member that binds activated LFA-1. However, none of these positions corresponds to claimed antibodies (it is not clear what numbering system Applicant uses). For Example, the specification on page 90, lines 12-16 discloses that an antibody can include a D2-57 light chain with one or more of the following substitutions (or insertion), e.g., at positions:G30S, L40P, A46L, L80P, W96ins, and S97T. However

none of these positions correspond to the D2-57 light chain of SEQ ID NO: 33, depicted on page 85 of the specification. Similarly, the positions of C1-54 and P1-G10, light chain, on page 91, lines 1-2 and 6-7 do not correspond to SEQ ID NOs: 34 and 35. Importantly, none of these variations alone or in combination with other variations have been shown to provide binding to the activated LFA-1.

Moreover, Brown et al (J. Immuno. 1996 May, 3285-91 at 3290 and Tables 1 and 2) describes how one amino acid change in the VH CDR2 of a particular antibody was tolerated whereas, the antibody lost binding upon introduction of two amino changes in the same region. Vajdos et al. (J. Mol. Biol. 2002, Jul 5, 320(2):415-28 at 416) teach that amino acid sequence and conformation of each of the heavy and light chain CDRs are critical in maintaining the antigen binding specificity and affinity which is characteristic of the parent immunoglobulin. Aside from the CDRs, the Fv also contains more highly conserved framework segments which connect the CDRs and are mainly involved in supporting the CDR loop conformations, although in some cases, framework residues also contact antigen. The scope of the claims encompasses antibodies with VH or VL that encompass variation (addition, deletion, substitution) in their FW and CDRs. The prior art discloses that 6 CDRs as being essential structure of antibody's binding site, and thus when intact, would provide enough structure to define the antibody's binding site (structure/function correlation) e.g., where amino acid substitutions can be made so as to change (e.g. 6CDR's) or retain (e.g., constant or variable framework) antigen binding. Neither the prior art not applicant's disclosure defines sufficient representative antibodies and/or sufficient structure/function correlation between modifying the VL or VH regions of the disclosed antibody and the retention of a specific binding member that binds activated LFA-1 to satisfy the WD requirement for the claims.

Claims 5 which is directed to a protein comprising the heavy chain variable domain sequence comprising SEQ ID NO:4 which has 9 variation out of 11 amino acids. The specification on page 92 provides exemplary variants that in the CDR3 region of the heavy chain from residues 96-120 of the DX-2001. The specification discloses that the aspartic acid at position 3 in CDR3 may interact with an Mg2+ ion bound to I-domain. This aspartic acid was conserved 75 of 80 different affinity matured Fabs (see page 93, lines 24-26). However, none of these variants have been shown to provide binding to the activated LFA-1 conformation. These variants had no specific VL domains paired with specific VH domains. Prior art methods do not result in an antibody solely by keeping CDR3 in the VH defined and randomizing the rest of the VH and VL domains.

The Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement make clear that the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics,

sufficient to show the applicant was in possession of the genus (Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001, see especially page 1106 3rd column).

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the written description inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.). Consequently, Applicant was not in possession of the instant claimed invention. See University of California v. Eli Lilly and Co. 43 USPQ2d 1398.

Applicant is directed to the Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

Applicant is invited to point to clear support or specific examples of the claimed invention in the specification as-filed.

12. Claims 1-11 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an anti-activated LFA-1 antibody comprising VH and/or VL of SEQ ID NOS: 34/33, 36/35, 38/37 or 61/60 (listed on page 85-86 of the specification); or an anti-activated LFA-1 antibody comprising VH CDR1-3 of SEQ ID NOS: 1-3 and VL CDR1-3 of SEQ ID NOs:7-9; or an anti-activated LFA-1 antibody produced by the cell line D2-57, DX-2001, C1-54 or P1-G10 (once the deposit is satisfied), does not reasonably provide enablement for the protein claimed in claims 1-11. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required to practice the claimed invention are summarized *In re Wands* (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). The factors most relevant to this rejection are the scope of the claim, the amount of direction or guidance provided, the lack of sufficient working examples, the unpredictability in the art and the amount of experimentation required to enable one of skill in the art to practice the claimed invention.

The knowledge in the art of making the genus of antibody that binds activated LFA-1 using a set of particular VH or VL CDRs as the starting point is low.

The scope of the claim encompasses antibodies with 6 intact CDRs as well as a subgenus of antibodies that encompass variation (fragments and/or analogs) in the 6 CDRs and framework. A subgenus of antibodies that encompass up to 10% to 20% variation in the VH and/or VL. A subgenus of antibodies that encompass up to 9 amino acid variations in the VH CDR3 of SEQ ID NO:4. A subgenus of antibodies that encompass less than

the full amino acid sequence of the VH CDR1-3 and/or VL CDR1-3 (i.e., 3/5, 13/17, 8/11, 7/11, 4/7 and/or 5/8, respectively.

However, neither the instant specification nor the prior art provide sufficient guidance or direction for one of ordinary skill in the art to make the antibodies encompassed by the breadth of the instant claims.

With respect to making the genus of anti-activated LAF-1 antibodies using a set of particular VH CDRs and/or VL CDRs as the starting point, e.g., SEQ ID NOs: 1-3 and/or CDR 7-9 as recited in claim 1, it is known in the art that antibody-antigen affinity and specificity is a function of not only direct CDR to antigen interactions, but also the interactions of the CDRs with framework residues in the same chain, e.g., VH CDR binding to VH framework residues, and in the opposing chain, e.g., VH CDR binding to VL framework residues. In addition, the CDR residues of each chain can interact with the CDRs of the opposite chain. It is for this reason that antibody humanization protocols, e.g., humanization of a murine antibody, provide extensive guidelines as to the retention of certain murine residues in the context of the human framework so as to preserve this web of interactions, the loss of any one of these interactions having the potential to ablate antibody-antigen binding (see, e.g., Eduardo Padlan, Mol Immunol. 1994 Feb;31(3):169-217, in particular column bridging paragraph on page 177; page bridging paragraph pages 178-179 through page 180; pages 201, 204 and Tables 8, 22 and 23 and Adair et al., United States Patent No. 5,859,205, in particular columns 1-6, 9-11 and 27-28).

It is also known that given one specified variable domain, either heavy or light, the skilled artisans can screen libraries to identify other variable domains that will pair with the starting variable domain and maintain antigen specificity (Portolano et al., J Immunol. 1993 Feb 1;150(3):880-7, see entire document, particularly figure 1). Thus, it is known in the art that artisans can screen for other variable domains that will ensure a functional antibody of defined antigen specificity if a full variable domain is used in the screening assay.

In the instant case, the claims recite only one of the 6 CDRs of a variable domain, not the all the 6 CDRs or the variable domain itself. While CDRs are important for binding and contribute the majority of contact residues with the target antigen, the framework residues are also essential for maintaining the proper antigen-binding conformation of the CDRs and for proper association of the heavy and light chain variable regions.

As such, it appears that making the claimed genus of antibodies would be an unpredictable endeavor requiring far more than routine experimentation because 3 CDRs comprise less than a majority of the residues important for antigen recognition, let alone a single CDR or a CDR variant. Moreover, art techniques for identifying other variable domains by screening require an intact variable domain comprising CDRs interspersed between frameworks as the starting structure to be taken through the screening assay. The instant claims recite less than this minimum structure that is required for screening,

and the instant specification fails to provide sufficient direction or guidance as to the breadth of the frameworks that can accommodate the claimed CDRs while simultaneously providing appropriate structure to pair with a light chain variable domain capable of acting with heavy chain variable domain to create an activated LFA-1 binding site.

The state of the prior art is such that it is well established in the art that the formation of an intact antigen-binding site of antibodies routinely requires the association of the complete heavy and light chain variable regions of a given antibody, each of which consists of three CDRs or hypervariable regions, which provide the majority of the contact residues for the binding of the antibody to its target epitope (Paul, Fundamental Immunology, 3rd Edition, 1993, pp. 292-295, under the heading "Fv Structure and Diversity in Three Dimensions"). The amino acid sequences and conformations of each of the heavy and light chain CDRs are critical in maintaining the antigen binding specificity and affinity, which is characteristic of the immunoglobulin. It is expected that all of the heavy and light chain CDRs in their proper order and in the context of framework sequences which maintain their required conformation, are required in order to produce an antibody having antigen-binding function and that proper association of heavy and light chain variable regions is required in order to form functional antigen binding sites (Paul, page 293, first column, lines 3-8 and line 31 to column 2, line 9 and lines 27-30). Even minor changes in the amino acid sequences of the heavy and light variable regions, particularly in the CDRs, may dramatically affect antigen-binding function as evidenced by Rudikoff et al (Proc. Natl. Acad. Sci. USA, 79(6):1979-1983, March 1982). Rudikoff et al teach that the alteration of a single amino acid in the CDR of a phosphocholine-binding myeloma protein resulted in the loss of antigen-binding function.

While there are some publications, which acknowledge that CDR3 is important, the conformations of other CDRs as well as framework residues influence binding. MacCallum et al (J. Mol. Biol., 262, 732-745, 1996) analyzed many different antibodies for interactions with antigen and state that although CDR3 of the heavy and light chain dominate, a number of residues outside the standard CDR definitions make antigen contacts (see page 733, right col.) and non-contacting residues within the CDRs coincide with residues as important in defining canonical backbone conformations (see page 735, left col.). The fact that not just one CDR is essential for antigen binding or maintaining the conformation of the antigen binding site, is underscored by Casset et al (Biochemical and Biophysical Research Communications, 307:198-205, 2003), which constructed a peptide mimetic of an anti-CD4 monoclonal antibody binding site by rational design and the peptide was designed with 27 residues formed by residues from 5 CDRs (see entire document). Casset et al also states that although CDR H3 is at the center of most if not all antigen interactions, clearly other CDRs play an important role in the recognition process (page 199, left col.) and this is demonstrated in this work by using all CDRs except L2 and additionally using a framework residue located just before the H3 (see page 202, left col.). Thus, the state of the art recognized that it would be highly unpredictable that a specific binding member comprising an antibody variable region but

comprising less than all six CDRs of a parental antibody. Thus, the minimal structure which the skilled artisan would consider predictive of the function of binding the activated LFA-1 includes six CDRs (three from the heavy chain variable region and three from the light chain variable region) from parental antibody D2-57 in the context of framework sequences which maintain their correct spatial orientation have the requisite activated LFA-1 binding function. One of ordinary skill in the art could not predictably extrapolate the teachings in the specification, limited to antibodies that comprise both the heavy chain variable region and the light chain variable region or all six CDRs (i.e., SEQ ID Nos:1-3 and 7-9) of D2-57 that binds the activated LFA-1 to make and use antibodies that comprise fewer than all six CDRs from parental antibody D2-57 (i.e., SEQ ID Nos:33-34), i.e., antibodies comprising a heavy/light chain variable region each having less than the required three CDRs as broadly as claimed. In cases involving unpredictable factors, such as most chemical reactions and physiological activity, more may be required. *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970) (contrasting mechanical and electrical elements with chemical reactions and physiological activity). See also *In re Wright*, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993); *In re Vaeck*, 947 F.2d 488, 496, 20 USPQ2d 1438, 1445 (Fed. Cir. 1991). This is because it is not obvious from the disclosure of one particular species, what other species will work. See MPEP 2164.03. One of skill in the art would neither expect nor predict the appropriate functioning of the anti- activated LFA-1 antibodies as broadly as is claimed.

Claim 5 recite that the protein binds activated LFA-1 has the heavy chain variable domains sequence comprises Xa-S-X2-D-X4-X5-S-X7-A-X8-X9-X10-X11 of SEQ ID NO: 4. However, the highly diverse VH CDR3 loops are the key determinant of specificity in antigen recognition in antibodies, and may allow the isolation of a new specificity. However, the specification fails to show which of the claimed amino acid or their combination would lead to a binding to activated LFA-1 protein. Given that the claimed antibody recognizes a conformational activated LFA-1 protein, the predictability of which amino acid or their combination that would lead to an antibody that would bind to the claimed activated LFA-1. Changes in the CDR3 sequence of the VH would deviate from the original antigen reactivity and specificity.

At issue is whether the claimed protein that binds activated LFA-1 would function as a pharmaceutical composition (intended use) in claim 11. The exemplification is drawn to the use of D2-57 to bind HA cells (cells expressing an LFA-1 with an I-domain locked in the high affinity conformation) relative to LA cells (cells expressing an LFA-1 with an I-domain locked in the low affinity conformation) (see Fig. 1 in particular). In view of the absence of a specific and detailed description in Applicant's specification of how to effectively use the pharmaceutical composition as claimed, and absence of working examples providing evidence which is reasonably predictive that the claimed pharmaceutical composition are effective for in vivo use, and the lack of predictability in the art at the time the invention was made, an undue amount of experimentation would be required to practice the claimed pharmaceutical composition with a reasonable expectation of success.

Reasonable correlation must exist between the scope of the claims and scope of the enablement set forth. In view on the quantity of experimentation necessary the limited working examples, the nature of the invention, the state of the prior art, the unpredictability of the art and the breadth of the claims, it would take undue trials and errors to practice the claimed invention.

13. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

12. Claims 1, 3, 4, 6-11 are rejected under 35 U.S.C. 102(b) as being anticipated by WO 98/23761 A1 as is evidenced by the specification on page 84, lines 1-7.

The `761 publication teaches and claims a humanized anti-CD11a antibody (LFA-1, CD11a/CD18) which binds specifically to human CD11a I-domain having a heavy chain variable domain sequence comprises a CDR2 that comprises at least 13 amino acids form YIWPSGGNTYYADSVKG (i.e., VISGDGGSTYYADSVKG, published SEQ ID NO: 11) and the light chain variable domain sequence comprises a CDR1 that comprises at least 7 amino acids from RASQSIGSYLN (i.e., RASQSISNYLA, see published SEQ ID NO: 13), A CDR2 that comprises at least 4 amino acids from AASSLQS (i.e., AASSLES, see published SEQ ID NO: 14) and a CDR3 that comprises at least 5 amino acids from QQSYSTPS (i.e., QQYNSLPWT, see published SEQ ID NO:15) (see published claims 1-17, 19 in particular). The humanized anti-CD11a antibodies bind to the I-domain of human CD11a with an affinity of about 1 $X10^{-8}$M or stronger. The antibody has an IC50 (nM) value of no more than about 1 nM for preventing adhesion of Jurkate cells to normal human epidermal keratinocytes expressing ICAM-1 or in a mixed lymphocyte response assay (see published claims 3-4). The `761 publication claims a chimeric construct (F(ab)2(lack Fc) domain) and humanized IgG1 of MHM2 (see claims 11-14). The `761 publication teaches pharmaceutical formulations comprising the antibody with physiologically acceptable carriers, excipients or stabilizers (see page 27, lines 20-21). The reference antibody which is derived from MHM24 antibody, binds to both HA (High affinity, activated LFA-1) and LA cells (un-activated, low affinity LFA-1) (see specification on page 84). The humanized antibody would compete with antibody D2-57, DX-2001, C1-54, or P1-G10 for binding to activated LFA-1 in the absence of evidence to the contrary.

Claims 1(iii-vi) are included because the mouse version of the MHM24 (IgG1) antibody (see Fig. 1 A-B of the `761) and claimed mouse D2-57 (IgG1) (see page 92, of the instant specification) share at least 95% homology. Accordingly, a nucleic acid encoding the MHM24 IgG1 antibody would hybridize to the D2-57 IgG1 antibody claimed, in the absence of evidence to the contrary.
The reference teachings anticipate the claimed invention.

13. Claims 1, 6-11 are rejected under 35 U.S.C. 102(b) as being anticipated by US 2002/0123614 A1 (of record).

The `614 teaches anti-LFA- 1 antibody, or an antigen binding fragment thereof (lacks an Fc domain), which selectively binds to an LFA-1 I-domain in the open conformation (see published claim 30) with high affinity fragment ¶59). The referenced antibody would compete with antibodies D2-57, DX-2001, C1-54, P1-G10 in the absence of evidence to the contrary. The `614 teaches a pharmaceutical composition comprising the antibody and a pharmaceutically acceptable carrier (published claim 28). The `614 publication teach that monoclonal antibodies BL5, F8.8, CBRLFA-1/9, May.035, TS1/22 and TS2/6 (full length IgG antibody) strongly inhibited binding of both wild-type and mutant K287C/K294C "activate or open" (¶202). The `614 teaches chimeric and humanized monoclonal antibodies, comprising both human and non-human portions, which can be made using standard recombinant DNA techniques, can also be used in the methods of the present invention (not immunogenic in humans) (¶86).

The reference teachings anticipate the claimed invention.

14. No claim is allowed.

15. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maher Haddad whose telephone number is (571) 272-0845. The examiner can normally be reached Monday through Friday from 7:30 am to 4:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on (571) 272-0735. The fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

September 17, 2009

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